PATENT COOPERATION TREATY

PCT/GB2004/005006

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

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Date of mailing (day/month/year) 08 June 2006 (08.06.2006)	
Applicant's or agent's file reference P36104A/CMU/MCM	IMPORTANT NOTICE

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2004/005006	26 November 2004 (26.11.2004)	26 November 2003 (26.11.2003)

Applicant
THE QUEEN'S UNIVERSITY OF BELFAST et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.+41 22 740 14 35	Authorized officer Dorothée Mülhausen Facsimile No.+41 22 338 87 40

Form PCT/IB/326 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P36104A/CMU/MCM	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/GB2004/005006	International filing date (*day/month/year*) 26 November 2004 (26.11.2004)	Priority date (*day/month/year*) 26 November 2003 (26.11.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE QUEEN'S UNIVERSITY OF BELFAST		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 17 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis*.2).

	Date of issuance of this report 29 May 2006 (29.05.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dorothée Mülhausen
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No. PCT/GB2004/005006	International filing date *(day/month/year)* 26.11.2004	Priority date *(day/month/year)* 26.11.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/11, A61K31/7088

Applicant
THE QUEEN'S UNIVERSITY OF BELFAST

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005006

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15, with reference to industrial applicability

because:

☒ the said international application, or the said claims Nos. 1-15, with reference to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005006

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-4, 13-17, 26-30, 39-41, 43, 44
	No: Claims	5-12, 18-25, 31-38, 42
Inventive step (IS)	Yes: Claims	1, 2, 16, 29
	No: Claims	5-15, 17-28, 30-44
Industrial applicability (IA)	Yes: Claims	16-44
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/005006

Reference is made to the following documents:

D1: HYER M.L. et al.: " Downregulation of c-FLIP sensitizes DU145 prostate cancer cells to Fas-mediated apoptosis " CANCER BIOLOGY & THERAPY, vol. 1, no. 4, July 2002, pages 401-406;

D2: USLU R. et al.: " Chemosensitization of human prostate carcinoma cell lines to anti-Fas-mediated cytotoxicity and apoptosis " CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 3, no. 6, June 1997, pages 963-972;

D3: THÉARD D. et al.: " Etoposide and Adriamycin but not Genistein can activate the checkpoint kinase Chk2 independently of ATM/ATR " BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 289, 2001, pages 1199-1204;

D4: GUROVA K.V. et al.: " Cooperation of two mutant p53 alleles contributes to Fas resistance of prostate carcinoma cells " CANCER RESEARCH, vol. 63, 1 June 2003, pages 2905-2912;

D5: IWASE M. et al.: " Enhanced susceptibility of oral squamous cell carcinoma cell lines to Fas-mediated apoptosis by Cisplatin and 5-Fluorouracil " INTERNATIONAL JOURNAL OF CANCER, vol. 106, 10 September 2003, pages 619-625;

D6: WAKASA T. et al.: " The combination of ionizing radiation and expression of a wild type p53 gene via recombinant adenovirus induced a prominent tumour suppressing effect in human oral squamous cell carcinoma " THE BRITISH JOURNAL OF RADIOLOGY, vol. 75, 2002, pages 657-662;

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/005006

D7: WO 03/035868 A (RIBOPHARMA AG (DE); WAJANT Harald; PFIZENMAIER Klaus; LIMMER Stefan; KREUTZER Roland; VORNLOCHER Hans-Peter) 1 May 2003;

D8: SIEGMUND D. et al.: " Selective inhibition of FLICE-like Inhibitory Protein (FLIP) expression with small interfering RNA oligonucleotides (siRNAs) is sufficient to sensitize tumor cells for TRAIL-induced apoptosis " MOLECULAR MEDICINE, vol. 8, no. 11, November 2002, pages 725-732;

D9: DATABASE EMBL-EBI 1 July 1999, " *Homo sapiens* FLICE-like inhibitory protein long form mRNA, complete CDs. " Database accession no. U97074;

D10: KAMARAJAN P. et al.: " Up-regulation of FLIP in cisplatin-selected HeLa cells causes cross-resistance to CD95/Fas death signalling " BIOCHEMICAL JOURNAL, vol. 376, no. 1, 15 November 2003, pages 253-260;

D11: MAY E. et al.: " Endogenous HeLa p53 proteins are easily detected in HeLa cells transfected with mouse deletion mutant p53 gene " ONCOGENE, vol. 6, no. 8, 1991, pages 1363-1366;

D12: PEDERSEN I.M. et al.: " The triterpenoid CDDO induces apoptosis in refractory CLL B cells " BLOOD, vol. 100, no. 8, 15 October 2002, pages 2965-2972;

D13: POULAKI V. et al.: " Fas-mediated apoptosis in neuroblastoma requires mitochondrial activation and is inhibited by FLICE inhibitor protein and bcl-2 " CANCER RESEARCH, vol. 61, 15 June 2001, pages 4864-4872.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/005006

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1). Claims **1-15** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1). Document D5 describes a method of killing oral squamous cell carcinoma (OSCC) cell lines NA and HSC-4, comprising administration to said cells of c-FLIP antisense oligonucleotides, CDDP (a platinum cytotoxic agent) and/or 5-FU, and the agonist Fas antibody CH-11 (see relevant passages throughout the entire article, in particular, see figure 6 and passages related thereto). Application of the results disclosed in this article for cancer therapy are also disclosed in D5.
HSC-4 cells harbour the p53 mutation Arg248Glu (see D6: pages 660-661).

The subject-matter of claims **5-12, 18-25, 31-38** is therefore not novel (Article 33(2) PCT; for claims 8, 9, 21, 22, 34 and 35, insofar as administration of 5-FU is concerned).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/005006

V.2). Document D10 describes a method of killing cancer HeLa cells comprising administration to said cells of (a) a c-FLIP antisense oligonucleotide and (b) cisplatin or Fas antibodies (D10: figures 6, 7 and relevant passages related thereto). HeLa cells contain no detectable p53 protein, due to HPV-mediated degradation of p53 itself (see D11: relevant passages throughout the entire article). Application of the results disclosed in this article for cancer therapy are also disclosed in D10.

The subject-matter of claim **42**, insofar as a kit comprising a platinum cytotoxic agent is concerned, is therefore not novel (Article 33(2) PCT).

V.3). Present claims **1-4, 13-17, 26-30, 39-41, 43, 44**, the parts of claims **8, 9, 21, 22, 34, 35** related to administration of oxaliplatin or CPT-11, and the part of claim **42** related to a kit comprising a thymidylate synthase inhibitor or a topoisomerase inhibitor, formally meet the requirements of Article 33(2) PCT because their subject-matter was not disclosed in the available prior art.

V.4). The subject-matter of claims 8, 9, 21, 22, 34 and 35 differs in part from the disclosure of D5 in that administration of oxaliplatin or CPT-11 is concerned.

The problem to be solved may therefore be regarded as the provision of a further platinum cytotoxic agents, to be used in a method of killing cancer cells.

The solution to this problem, as claimed in present claims **8, 9, 21, 22, 34** and **35** cannot be considered as involving an inventive step for the following reasons: the compounds oxaliplatin and CPT-11 can be considered equivalent in their scope to the compound CDDP, and can be interchanged with this latter compound where circumstances make it desirable. They therefore represent merely some of several

straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem of finding alternative platinum cytotoxic agents.

V.5). The subject-matter of claims 14, 15, 27, 28, 40, 41, 43 and 44 differs in part from the disclosure of D5 in that interfering RNA oligonucleotides are concerned.

The problem to be solved may therefore be regarded as the provision of further c-FLIP inhibitory agents.

The solution to this problem, as claimed in present claims **14, 15, 27, 28, 40, 41, 43** and **44** (for claims 15, 28, 41, 43 and 44, insofar as an RNAi agent having nucleotide sequence as from SEQ ID NO:1 is concerned) cannot be considered as involving an inventive step for the following reasons: small interfering RNA oligoribonucleotides can be considered equivalent in their scope to antisense oligonucleotides, and can be interchanged with these latter where circumstances make it desirable (see for example document D7, and its corresponding article D8, D9 being the c-FLIP sequence cited by D8).

They therefore represent merely some of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem of finding alternative c-FLIP inhibitors. Concerning the RNAi agent having nucleotide sequence as from SEQ ID NO:1, concerned in present claims 15, 28, 41, 43 and 44, it should be remarked that document D7 and D8 disclose an RNAi agent whose sequence overlaps partially with